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ALCOHOLISM CLINICAL & EXPERIMENTAL RESEARCH

ORIGINAL ARTICLE

Common and distinct neural connectivity in attention-deficit/hyperactivity disorder and alcohol use disorder studied using resting-state functional magnetic resonance imaging

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Abstract

Background: A link between attention-deficit/hyperactivity disorder (ADHD) and alcohol use disorder (AUD) has been widely demonstrated. In this study, we used neuroimaging to investigate the connectivity traits that may contribute to the comorbidity of these disorders.

Methods: The study included an AUD group (*N* = 18), an ADHD group (*N* = 17), a group with AUD + ADHD comorbidity (*N* = 12) and a control group (*N* = 18). We used resting-state functional connectivity in a seed-based approach in the default mode networks, the dorsal attention network, and the salience network.

Results: Within the default mode networks, all affected groups shared greater connectivity toward the temporal gyrus when compared to the control group. Regarding the dorsal attention network, the Brodmann area 6 presented greater connectivity for each affected group in comparison with the control group, displaying the strongest aberrations in the AUD + ADHD group. In the salience network, the prefrontal cortex showed decreased connectivity in each affected group compared to the control group.

Conclusions: Despite the small and unequal sample sizes, our findings show evidence of common neurobiological alterations in AUD and ADHD, supporting the hypothesis that ADHD could be a risk factor for the development of AUD. The results highlight the importance of an early ADHD diagnosis and treatment to reduce the risk of a subsequent AUD.

KEYWORDS
alcohol use disorder, default mode network, dorsal attention network, salience network

Farré-Colomés and Gerhardt equally contributed to this work.

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INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is defined as a developmental behavioral disorder characterized by inattentiveness and impulsiveness (American Psychiatric Association, 2013) and in most of the cases becomes symptomatic during childhood. Despite the symptoms tending to improve with age, many adults continue to experience ongoing deficits (Sibley et al., 2017). A high prevalence of adult ADHD has been reported in alcohol use disorder (AUD) patients (20.5% in a German population (Luderer et al., 2018)). Most of these cases were never diagnosed before (van Emmerik-van Oortmerssen et al., 2012; Huntley et al., 2012). The reasons underlying this prevalence remain unknown, although ADHD traits such as impulsivity have already been correlated with the frequency of alcohol intake in ADHD individuals (Weafer et al., 2011). This indicates a predisposition of excessive alcohol use in ADHD that could lead to an increased risk for developing an AUD. ADHD as a risk factor for later substance use disorder (SUD) has been discussed previously (Lee et al., 2011; Shoham et al., 2019; Wilens et al., 2011). Stimulant ADHD medication may even protect against later SUD (Chang et al., 2014). Contrary findings are sparse. However, adults with remitted ADHD symptoms do not differ from healthy controls, that were never diagnosed with ADHD regarding an SUD outcome in later life (Breyer et al., 2014). A recent meta-analysis also revealed that comorbid conduct or oppositional defiant disorders contribute to, but not fully, explain an increase of SUD in later life (Groenman et al., 2017).

The default mode network (DMN) was initially described as a network of interacting brain regions, active during wakeful rest (Buckner et al., 2008). It has also been suggested that the DMN is involved in attention regulation—higher demanding tasks lead to a gradually decreasing connectivity (Buckner et al., 2008; Fassbender et al., 2009; Posner et al., 2014; Raichle & Snyder, 2007). It is composed of 3 main interconnected nodes: the posterior cingulate cortex (PCC), the angular gyrus, and the medial prefrontal cortex (mPFC) (Andrews-Hanna et al., 2014), see Figure 1. Previous studies on resting-state functional connectivity (rsFC) in ADHD have noticed an impaired connectivity within the DMN, presenting higher connectivity values than control groups (Cao et al., 2009; McCarthy et al., 2013; Sripada et al., 2014b; Tomasi & Volkow, 2012). The PFC is associated with impulse control and social inhibition (Hesslinger et al., 2002). Lesions within this area can cause ADHD-like symptoms. This was supported by further findings regarding general decreased activity in the inferior PFC of ADHD individuals during different tasks (Arnsten & Rubia, 2012). Abnormal DMN functioning can therefore explain part of the ADHD symptoms (Castellanos et al., 2008), that is, to sporadic attention lapses and decreased cognitive performance (Li et al., 2007; Posner et al., 2014; Weissman et al., 2006). Enhanced connectivity within the DMN has also been found in AUD populations (Kamarajan et al., 2020; Owens et al., 2019; Zhu et al., 2017). Regarding AUD, enhanced connectivity in the DMN was linked to impaired self-awareness, negative emotions, and negative ruminations. The DMN seems to be highly involved during withdrawal phases of addiction (Zhang & Volkow, 2019), associated with stronger craving and stress-related relapse. Other studies have suggested a possible relation between DMN and hyperactivity and impulsivity scores in AUD (Kamarajan et al., 2020; Zhu et al., 2017) and also greater connectivity between the DMN and the executive control and salience networks (Owens et al., 2019).

The dorsal attention network (DAN) is involved in top-down regulation and task-related attention (Corbetta et al., 2000; Majerus et al., 2018; Shulman et al., 2009; Todd et al., 2005) and therefore crucial for attention control. It is composed of the bilateral intraparietal sulci (IPS) and frontal eye fields (FEF) (Vossel et al., 2014), see Figure 1. The relation between this specific attention network and ADHD is still ambiguous. Decreased rsFC has been described in ADHD within the DAN (Bush, 2010; Gao et al., 2019; Sidlauskaite et al., 2016; Tomasi & Volkow, 2012; Zhou et al., 2019) and was further correlated to high levels of ADHD symptoms (McCarthy et al., 2013). Regarding AUD, previous fMRI studies have described an

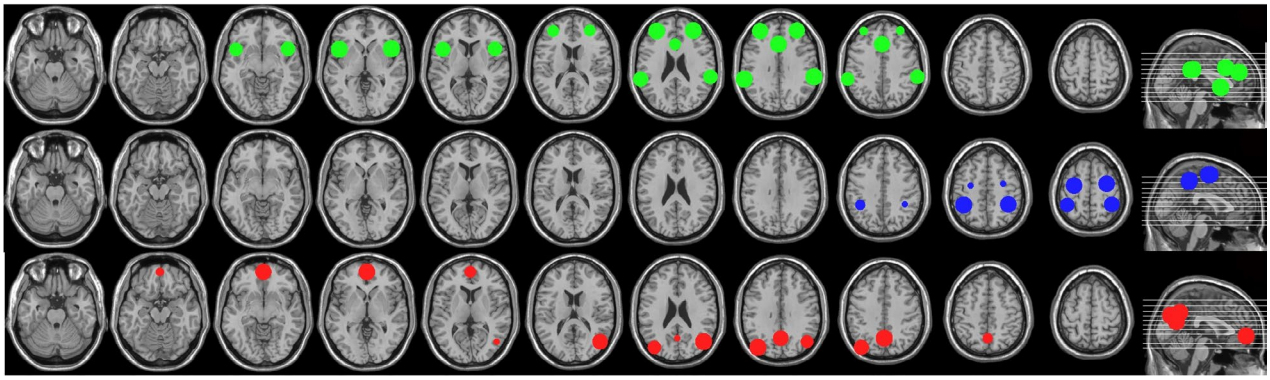

FIGURE 1 Schematic display of examined resting-state networks and corresponding nodes. Top: Salience network including the anterior cingulate cortex (0, 22, 35), anterior insula right (47, 14, 0) and left (−44, 13, 1), the rostal prefrontal cortex right (32, 46, 27) and left (−32, 45, 27) and the supramarginal gyrus right (62, −35, 32) and left (−60, −39, 31). Middle: Dorsal attention network including the frontal eye fields right (30, −6, 64) and left (−27, −9, 64) and the intraparietal sulcus right (39, −42, 54) and left (−39, −43, 52). Down: Default mode network including the middle prefrontal cortex (1, 55, −3), lateral parietal right (47, −67, 29) and left (−39, −77, 33) and the posterior cingulate cortex (1, −61, 38). Spheres were drawn around peak voxel (MNI coordinates) to illustrate the brain regions [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Mean (SD) group characteristics of all participants (*N* = 61). Questionnaire data from maximum *N* = 54 participants (AUD = 13, ADHD = 15, AUD + ADHD = 9, Control = 18)

	AUD	ADHD	AUD + ADHD	Control	ANOVA[a]/Welch[b]
N	17	16	10	18	
Male:Female	15:2	12:4	7:3	12:6	$\chi^2(3) = 2.41$, $p = 0.492$
Education (years)*	12.5 (2.1)	14.1 (2.2)[1]	11.8 (1.6)[1]	14.2 (2.9)	$F(3, 48) = 3.476$. $p = 0.023$[a]
Age*	48.29 (11.20)[1]	31.00 (10.55)[1]	41.10 (11.30)	40.72 (13.83)	$F(3, 57) = 5.837$. $p = 0.002$[a]
Smoker [yes:no:unknown]	9:3:5	2:12:2	8:1:1	1:15:2	$\chi^2(3) = 26.71$, $p = 0.000$
FTND*	6.11 (1.17)[1,2]	2.40 (2.61)[1]	4.89 (2.42)[3]	0 (0)[2,3]	$F(3, 23) = 11.159$, $p = 0.000$[a]
AUQ*	12.62 (6.67)	8.36 (0.84)	12.78 (5.31)	9.94 (3.39)	$F(3, 20) = 4.461$, $p = 0.015$[b]
AUDIT*	26.77 (4.64)[1,2]	2.81 (4.32)[1,3]	23.00 (8.06)[3,4]	3.03 (2.29)[2,4]	$F(3, 21) = 108.679$, $p = 0.000$[b]
ADS*	16.24 (5.58)[1,2]	2.93 (4.32)[1,3]	13.22 (4.91)[3,4]	2.44 (2.85)[2,4]	$F(3, 49) = 34.957$, $p = 0.000$[a]
Abstinence (days)*	20.9 (12.2)	46.6 (79.4)	21.4 (19.1)	17.6 (25.1)	$F(3, 23) = 0.525$, $p = 0.670$[b]
WURS-k					
Attention-deficit/ hyperactivity*	6.75 (6.18)[1,2]	17.36 (5.99)[1,3]	19.67 (7.12)[2,4]	5.28 (5.04)[3,4]	$F(3, 49) = 19.360$, $p = 0.000$[a]
Impulsivity*	1.92 (1.93)[1,2]	6.50 (4.81)[1,3]	9.33 (3.61)[2,4]	1.28 (1.71)[3,4]	$F(3,21) = 16.262$, $p = 0.000$[b]
ADHD-SR					
Attention deficits*	3.25 (3.60)[1,2]	18.50 (4.11)[1,3]	16.44 (6.44)[2,4]	2.61 (2.50)[3,4]	$F(3, 21) = 60.604$, $p = 0.000$[b]
Hyperactivity*	2.25 (2.86)[1,2]	6.21 (5.09)[1,3,4]	11.00 (2.35)[2,3,5]	0.56 (0.78)[4,5]	$F(3, 18) = 57.349$, $p = 0.000$[b]
Impulsivity*	1.33 (1.56)[1,2]	5.79 (3.62)[1,3]	7.33 (3.04)[2,4]	0.78 (1.00)[3,4]	$F(3, 20) = 19.289$, $p = 0.000$[b]
Overall score*	6.83 (6.07)[1,2]	30.50 (7.96)[1,3]	34.78 (9.32)[2,4]	3.94 (3.42)[3,4]	$F(3, 20) = 66.077$, $p = 0.000$[b]

Note: Superscript * indicates the descriptive measures mean (M) and standard deviation (SD). Superscript letters indicate the statistical test used for group comparisons (ANOVA[a]/ Welch[b]) and describe significant post hoc test results ([1, 2, 3, 4], $p < 0.05$) with respect to the group. Smoker: expected count less than 5 in 25% of cells.

Abbreviations: ADHD-SR, ADHD self-report scale; ADS, Alcohol Dependence Scale; AUDIT, Alcohol Use Disorder Identification Test; AUQ, Alcohol Urge Questionnaire; FTND, Fagerström Test for Nicotine Dependence; WURS-k, German short version of the Wender Utah Rating Scale.

attentional bias in response to alcohol cues (Schacht et al., 2013; Vollstädt-Klein et al., 2012). For this reason, substance-dependent individuals show enhanced attention toward substance-related cues, causing increased craving (Loeber et al., 2009). However, brain regions and connectivity impairments involved in attention alterations in AUD have been barely described.

The salience network (SN) has also been reported to be altered in ADHD and AUD. The functions of this network are related to the integration of internal and external information to guide behavior (Menon & Uddin, 2010) and detecting behaviorally relevant stimuli to coordinate neural resources (Uddin, 2015). The SN is composed of 2 main nodes: the anterior insula (AI) and the anterior cingulate cortex (ACC) (Menon & Uddin, 2010), see Figure 1. The involvement of the SN in focusing attention and guiding behavior is directly related to ADHD main characteristics: inattentiveness and impulsivity. ADHD is associated with increased rsFC within the SN and weakened connectivity toward other networks, such as the DMN (Sidlauskaite et al., 2016; Tomasi & Volkow, 2012). Task-related neuroimaging studies regarding emotion processing observed altered salience processing that led to higher distractibility in ADHD (Vetter et al., 2018). Furthermore, a positive relation between ADHD symptom load and connectivity strength between the dorsal ACC and the AI was observed in nicotine-dependent participants (Janes et al., 2018). The involvement of the SN in assimilating internal and external information to guide behavior (Menon & Uddin, 2010) becomes important in SUD due to the demonstrated influence of internal salient stimuli (like craving and withdrawal) and external cues on the motivation for drug use. Other neuroimaging studies found a generalized enhanced connectivity within the SN and disrupted connectivity between the DMN and the SN in SUD (Owens et al., 2019; Zhang & Volkow, 2019; Zhu et al., 2017). High impulsivity has been described in AUD (Bjork et al., 2004; Soloff et al., 2000; White et al., 2011) correlating it with low activation of the ventral striatum and ACC (Beck et al., 2009). Increased rsFC within the SN and impulsivity traits have been suggested as possible markers of AUD severity (Kamarajan et al., 2020; Weafer et al., 2011; Zhu et al., 2017).

The above-described observations suggest similar alterations for both disorders in the rsFC. Several studies have approached these impairments separately for both disorders but have never compared them directly. This study offers a new perspective on the rsFC in AUD and ADHD, providing analyses of individuals with comorbid diagnoses of ADHD and AUD for the first time. Following previous results on this subject showing an existing relation between ADHD symptoms and SUD propensity (Bjork et al., 2004; Brinkman et al., 2015; Daurio et al., 2018; van Emmerik-van Oortmerssen et al., 2012; Knop et al., 2009; Lee et al., 2011; Weafer et al., 2011), the aim of the study was to examine shared rsFC traits that may explain the higher vulnerability to AUD in individuals with ADHD. We

hypothesized that the previously observed increase and decrease of rsFC in above-mentioned networks become also apparent in our sample (namely AUD and ADHD groups). We further hypothesize that alterations in rsFC regarding these networks are even more pronounced in comorbid individuals (AUD + ADHD). We discuss whether the existence of connectivity impairments shared in both disorders could explain the comorbidity rates in the general population. Using a group comparison analysis, individuals with AUD, ADHD, both diagnoses (AUD + ADHD), and healthy controls (HC) were examined and compared under a rsFC approach.

MATERIALS AND METHODS

Participants

The study examined 65 adult participants between October 2014 and June 2017. All individuals started with a screening procedure for both AUD and ADHD. Individuals included in the AUD group were diagnosed with at least moderate AUD (according to DSM-5 (American Psychiatric Association, 2013)), which corresponds to former DSM-IV nomenclature "dependence" (Dawson et al., 2013). For a detailed description of recruiting, diagnostic, and exclusion process, see the Supplementary Material and Figure S1. After being included in the study and assigned to 1 of the 4 groups, participants had to fill out a battery of questionnaires prior to the fMRI experiment, including the Alcohol Dependence Scale (Skinner & Horn, 1984), the Alcohol Use Disorder Identification Test (Reinert & Allen, 2002), the Alcohol Urge Questionnaire (Bohn et al., 1995), the German version of the Wender Utah Rating Scale (Retz-Junginger et al., 2002), the ADHD self-report scale (Rösler et al., 2008), and the Fagerström Test for Nicotine Dependence (Heatherton et al., 1991). Additionally, demographic variables and history of drug consumption were assessed. The AUD group included 18 individuals, the ADHD group 17, the AUD + ADHD group 12, and the control group 18. For details on the final sample, please see Table 1. The study was approved beforehand by the Ethics Committee of the Medical Faculty in Mannheim, Heidelberg University (approval number 2013-530 N-MA). All participants granted written informed consent according to the Declaration of Helsinki.

FMRI acquisition

Scanning was performed with a 3 T whole-body tomography (MAGNETOM Trio with TIM Technology; Siemens, Erlangen, Germany). Participants were instructed to keep their eyes closed during the 6:06 minutes resting-state fMRI. Further, they were instructed to let their thoughts wander, not to think of anything in particular, and not to hold on longer to any thoughts. T2*-weighted echo-planar images (EPI) were acquired in a transversal orientation 30° clockwise to AC-PC-line covering the whole brain. Parameters were as follows: TR = 1.5 s, TE = 28 ms, flip angle = 80°, 24 slices, slice thickness 4 mm, 1 mm gap, voxel dimensions 3 × 3 × 5 mm^3, FOV 192 × 192 mm^2, 64 × 64 in-plane resolution. This short TE and the 30° flip to AC-PC orientation were chosen to minimize susceptibility artifacts. The number of images measured for each subject was 240. In addition, a T1-weighted 3D MPRAGE dataset consisting of 192 sagittal slices (slice thickness 1 mm, 1 × 1×1 mm voxel size, FOV 256 × 256 mm^2, TR = 2300 ms, TE = 3.03 ms, TI = 900 ms, flip angle = 9°) was acquired.

FMRI preprocessing

Imaging data were preprocessed with the CONN toolbox v18a (Whitfield-Gabrieli & Nieto-Castanon, 2012) (https://www.nitrc.org/projects/conn), running in MATLAB R2017a through SPM12 (Wellcome Department of Imaging Neuroscience, London, UK). The first twenty scans were excluded to prevent artefacts caused by magnetic saturation. Both structural and functional images were preprocessed using the default pipeline for volume-based analysis provided by the CONN toolbox. This pipeline incorporates multiple steps, including realignment and unwarping (with subject motion estimation and correction), centering, slice-time correction, outlier detection with ART-based (Artifact Detection Tools) identification for scrubbing using conservative settings (95^{th} percentiles), segmentation (white matter, gray matter, and cerebral spinal fluid), normalization according to the Montreal Neurological Institute atlas, and smoothing at 8 mm full width half maximum (FWHM) Gaussian kernel. After the preprocessing steps, the default blister variables given by the CONN toolbox were regressed out of the signal. Data were then filtered through a 0.008–0.09 Hz band-pass and linear trends were removed using lineal detrending additional step. A quality check was performed using the same CONN toolbox features. Data of individuals with inappropriate head movement (>3 mm/3°) and/or other artifacts were discarded. Consequently, 4 participants were excluded from further analysis.

Statistical analysis

The statistical analysis started with a seed-to-voxel connectivity analysis. Seed networks, predefined by the CONN toolbox, were selected based on their relevance in AUD and ADHD disorders, according to previous literature: The DMN, DAN, and SN were chosen, see Figure 1. Images derived from the first-level analysis were then used to compare network activity during rest between groups. Seed-to-voxel analysis was used to identify differential network activation between the predefined groups. Using the CONN toolbox, the seeds were located in the predefined networks: posterior cingulate cortex (PCC) for the DMN, frontal eye fields (FEF) for the dorsal attention, and anterior cingulate cortex (ACC) for the salience network. The PCC is the most commonly used seed to study the DMN, since it is the greatest node of the

connectivity and has been described to best define this network (Fransson & Marrelec, 2008). Additionally, many studies focusing on SUD reported functional impairments at rest within this area (Kamarajan et al., 2020; Müller-Oehring et al., 2015; Weber et al., 2014; Zhang & Volkow, 2019), and it has been repeatedly demonstrated that it is also altered in ADHD (Castellanos et al., 2008; Fair et al., 2010; Posner et al., 2014; Salmi et al., 2018). ACC has been described as a key region of cue processing in AUD patients showing altered FC when alcohol-related images were shown to patients (Alba-Ferrara et al., 2016). It was further related to self-control impairments in AUD patients and has been positively correlated with their degree of alcoholism (Arienzo et al., 2020). Studies regarding rsFC in AUD defined important connectivity alterations within this area (Müller-Oehring et al., 2015). Also, ADHD individuals have been widely described to show rsFC impairments within the ACC (Castellanos et al., 2009; Posner et al., 2014; Sidlauskaite et al., 2016). Previous studies mostly used the inferior parietal sulcus (IPS) as the seed to study the DAN. We decided to choose the FEF as a DAN seed region because it is involved in working memory processing and sustained attention (Offen et al., 2010) which are both relevant in AUD and ADHD even though, only 1 study has reported significant rsFC aberrations at the FEFs in ADHD individuals (Shulman et al., 2009). Connectivity within the selected networks was compared between the established groups using volume-based connectivity. To assess the relationship between rsFC and clinical variables, we performed supplementary regression analyses in SPM12. We used images derived from the first-level analyses with the CONN toolbox, for the 3 networks. ADHD- and AUD-related measures included the sub score for impulsivity, as this feature is relevant for both, AUD and ADHD, the overall score of the Adult ADHD Self-Report Scale (Kessler et al., 2005), and the Alcohol Use Disorder Identification Test (Reinert & Allen, 2002), respectively. Due to missing questionnaire data (see limitations), N = 53 individuals were included (AUD = 12, ADHD = 14, AUD + ADHD = 9, HC = 18). Age was included as a covariate of no interest in all analyses. To control for multiple statistical testing, the probability of a family-wise error (FWE) was set to 0.05. For this purpose, we used the AlphaSim method implemented in the NeuroElf toolbox (www.neuroelf.net). A voxelwise threshold of $p < 0.005$ was combined with a cluster extent threshold of 60 voxels, determined by AlphaSim using 25000 Monte Carlo simulations for the second-level analyses of both, the seed-to-voxel analyses and regression analyses. Estimation of smoothness based on the residual images was conducted using SPM by taking the maximum of the 3 estimated parameters in x, y, and z direction.

RESULTS

The number of individuals used for the rsFC analysis was 61 out of the 65 participants initially included in the study. Therefore, groups were composed of 17 individuals with AUD, 16 individuals with ADHD, 10 individuals with AUD + ADHD, and 18 healthy controls. The main reason for excluding was excessive head movement during the scanning session or other technical reasons. Other participants did not meet the inclusion criteria due to reported drug or medication intake (see CONSORT diagram, Figure S1). Questionnaire scores and characteristics of the analyzed sample, with respect to the different groups, are displayed in Table 1. The group allocation was successfully confirmed by questionnaires addressing AUD and/or ADHD symptoms.

Default mode network

To analyze this network, the seed was located in the PCC. Enhanced connectivity to the middle temporal gyrus (MTG) was observed in ADHD and AUD compared to HC (see Tables S1 and S2). These comparisons further showed increased connectivity to the supramarginal gyrus (SMG) (see Figure 2). The comparison between AUD and ADHD displayed an enhanced activation in the ADHD group to the caudate and putamen (see Table S3). In the AUD + ADHD group comparisons, the reported heightened connectivity was also reaching areas of the inferior temporal gyrus (ITG) (see Figure 3). The AUD + ADHD group exhibited increased connectivity values in the same temporal area (BA 20) when compared to the HC and to the ADHD group, but displaying smaller clusters (see Tables S4 and S7). Furthermore, when compared to HC, the AUD + ADHD group also presented enhanced connectivity to the SMG (BA40) and decreased connectivity to the parahippocampal gyrus and hippocampus (see Table S5). The AUD + ADHD group displayed a much bigger cluster in this area than any of the other disorder group. The Brodmann areas 4 and 6 (BA 4 and 6) were also observed to have weakened connectivity in the AUD + ADHD group compared to both, the HC and the AUD group (see also Table S6).

Dorsal attention network

Using the FEF as a seed, several comparisons revealed increased connectivity to the BA 6 (see Figure 4), when comparing the AUD + ADHD group and the ADHD group to the other groups (see Tables S9, S10 and S11). The supplementary motor area (SMA) is especially altered in the ADHD and AUD + ADHD groups, showing higher activation in the AUD + ADHD group when compared to the ADHD. Therefore, individuals with AUD + ADHD showed enhanced connectivity to the BA 6 compared to HC and AUD. In addition, the comparison between ADHD and HC also displayed a heightened connectivity within this area in ADHD. Further, the fusiform gyrus displayed higher connectivity values in AUD + ADHD in comparison to HC and to the ADHD, but ADHD group reported lower connectivity than HC (see Table S8) The AUD + ADHD group also exhibited higher connectivity to the Insula than the HC and the AUD group.

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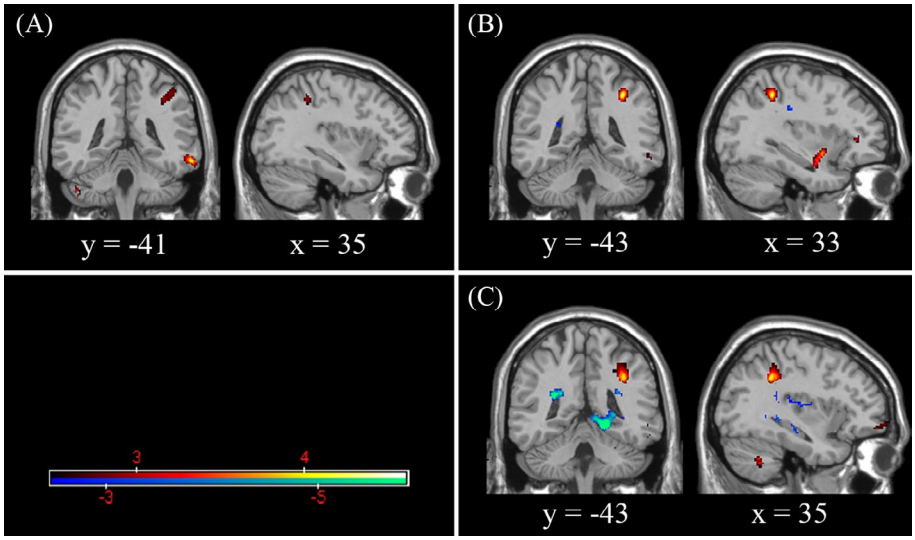

FIGURE 2 Comparison of resting-state connectivity for the DMN with the PCC as seed. Increased connectivity in the supramarginal gyrus (SMG) in AUD (A), ADHD (B), and AUD + ADHD (C) compared to HC. *p*-level <0.005 / *k* ≥ 60 voxel [Color figure can be viewed at wileyonlinelibrary.com]

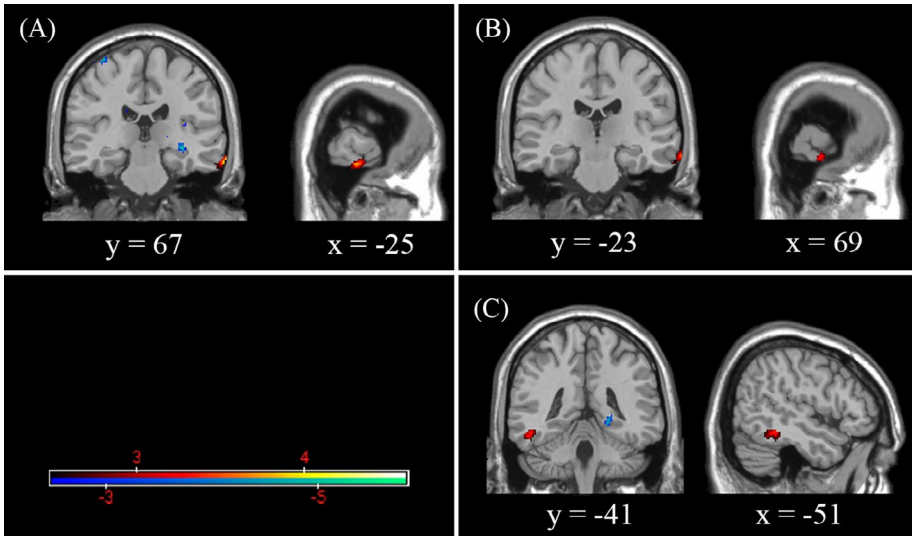

FIGURE 3 Comparison of resting-state connectivity for the DMN with the PCC as seed. Increased connectivity in the Inferior temporal gyrus (ITG) in the ADHD + AUD group compared to the HC (A) and to the ADHD group (B, C). *p*-level <0.005 / k ≥ 60 voxel [Color figure can be viewed at wileyonlinelibrary.com]

Salience network

To examine the SN, the ACC was used as the seed. Two areas in this network were found to be relevant. Regarding the medial orbitofrontal cortex (OFC) (see Figure 5), decreased connectivity was observed for all groups compared to the HC, with a shared focus on the OFC and other parts of the PFC (see Tables S13, S15, and S17). Additionally, decreased connectivity within this same area was observed in the AUD + ADHD group when compared to AUD. Furthermore, the other main area affected was the SMG (see Figure 6). For this region, AUD and ADHD presented higher connectivity than HC (see Tables S12 and S14), whereas the AUD + ADHD group displayed reduced connectivity compared to AUD or ADHD (see Tables S19 and S20). Importantly decreased connectivity to the basal ganglia was also observed for the AUD + ADHD group compared to HC, including the hippocampus, the putamen, and the lentiform nucleus.

Between networks connectivity

Overall, several brain areas have been found to display connectivity alterations in different networks. The BA 6 was reported to have decreased connectivity in the DMN for the AUD + ADHD group when compared to HC and to AUD (see Tables S5 and S6), but in the DAN (see Tables S9 and S10), and in the SN (see Tables S16 and S18), this

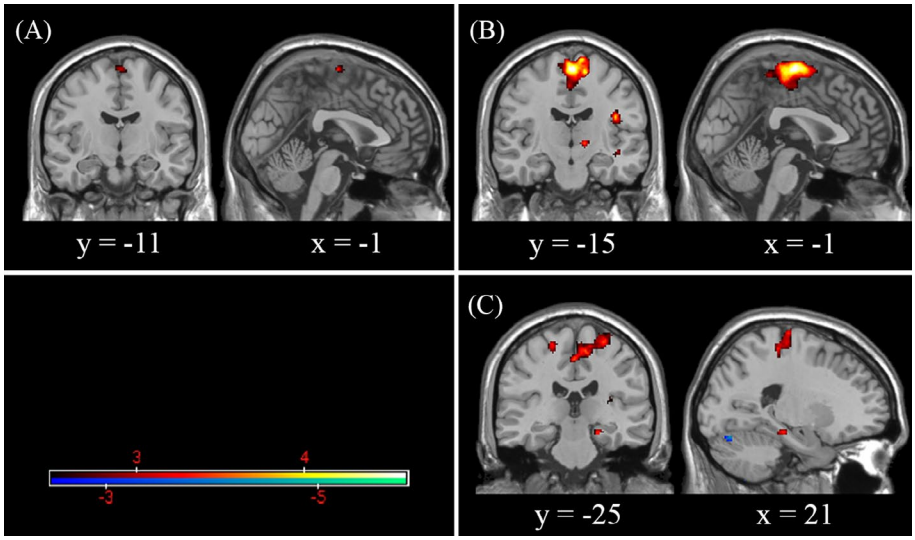

FIGURE 4 Comparison of resting-state connectivity for the DAN with the FEF as a seed. Increased connectivity in the BA 6 in the ADHD group (A) and especially in the AUD + ADHD (B) group when compared to HC. The AUD + ADHD group displayed increased connectivity also when compared to the AUD (C). *p*-level <0.005 / k ≥ 60 voxel [Color figure can be viewed at wileyonlinelibrary.com]

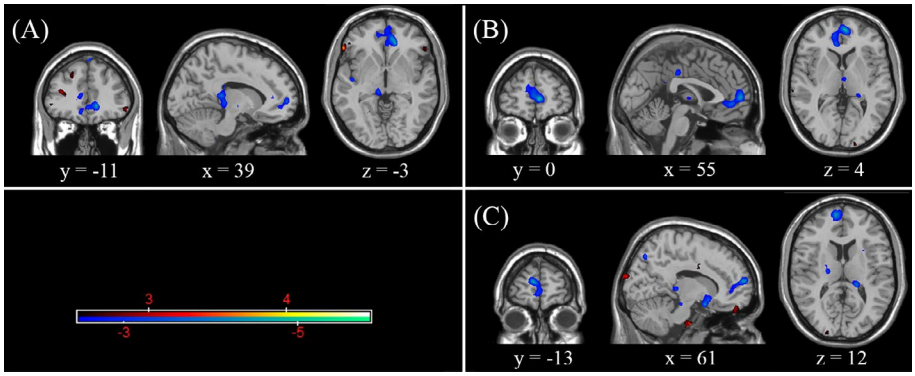

FIGURE 5 Comparison of resting-state connectivity for the SN with the ACC as a seed. Decreased connectivity in the orbitofrontal cortex (OFC) and other parts of the prefrontal cortex (PFC) has been found in all the groups compared to HC. The AUD (A), the ADHD (B), and the AUD + ADHD (C) groups show similar connectivity patterns when compared to the HC. *p*-level <0.005 / *k* ≥ 60 voxel [Color figure can be viewed at wileyonlinelibrary.com]

area displayed increased connectivity in the same group comparisons. Moreover, the SMG also showed interesting, shared connectivity patterns. This area was reported to have increased connectivity in the DMN for the AUD and the ADHD groups when compared to HC (see Tables S1 and S2). The SN showed the same pattern of increased connectivity in the AUD and the ADHD groups compared to HC (see Tables S12 and S14). Furthermore, the AUD + ADHD group showed increased connectivity even compared to AUD and ADHD. However, the DAN was reported to have decreased connectivity in the ADHD group compared to HC (see Table S8).

Clinical measures of ADHD and AUD in relation to rsFC

Relating AUD or ADHD severity to rsFC, by using the Alcohol Use Disorder Identification Test (AUDIT) scores and the overall and impulsivity scores of the ADHD self-rating scale (ADHD-SR), resulted in positive and negative correlations. These correlations allowed to associate the reported group differences with the severity of the disorder.

The connectivity of the DMN presented a positive correlation with the AUDIT score in the MTG and SMG, but no negative correlation was related to our rsFC results. The impulsivity and overall scores of ADHD-SR scale showed a positive correlation with the MTG. No negative correlation was found for the impulsivity scores, but the overall scores correlated with the rsFC in the Insula and Hippocampus (see Tables S21–S24).

Regarding the DAN, a positive correlation of the rsFC with the AUDIT score was observed in the BA 6, but no negative correlation was related to our rsFC results. The impulsivity scores of the ADHD-SR scale displayed a positive correlation with the rsFC in the BA 6, as did the overall scores but also showing a positive correlation to the fusiform gyrus and the insula. However, no negative

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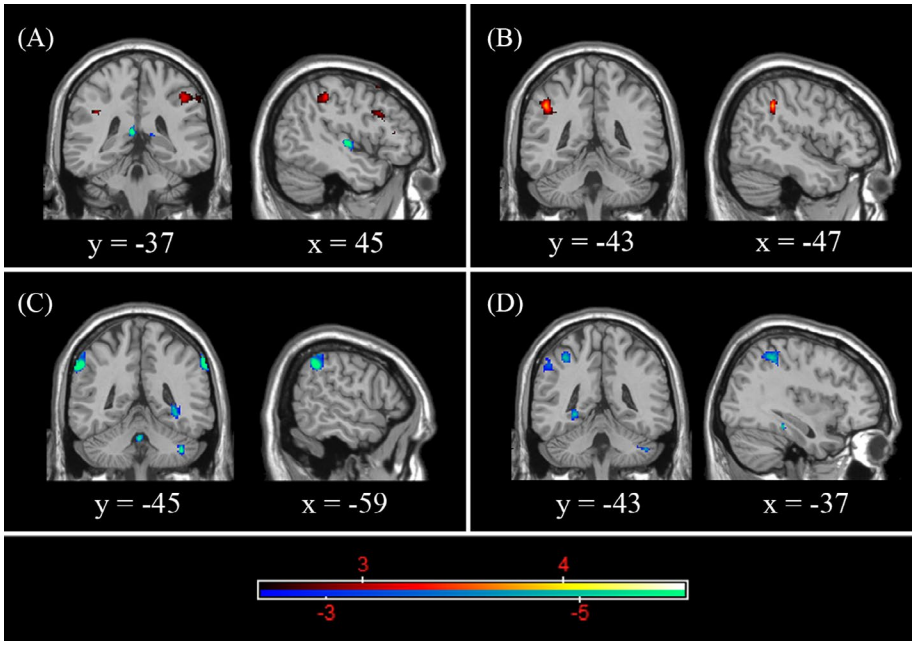

FIGURE 6 Comparison of resting-state connectivity for the SN with the ACC as seed. Increased connectivity in the supramarginal gyrus (SMG) in AUD (A) and ADHD (B) compared to the HC, but in the AUD + ADHD group the activity is reported to be lower than in both groups when compared to the AUD (C) and ADHD (D) groups. *p*-level <0.005 / $k \geq 60$ voxel [Color figure can be viewed at wileyonlinelibrary.com]

correlation with our results was described for any of the ADHD-SR scale scores (see Tables S25–S27).

For the SN, a positive correlation of the results in rsFC with the AUDIT score was reported in the SMG. Moreover, this network also exhibited a negative correlation with this score in the OFC, putamen, hippocampus, and lentiform nucleus. Regarding the impulsivity scores of the ADHD-SR scale, a positive correlation with the rsFC of the network was found in the SMG, but no positive correlation was described for the overall score. Instead, both scores of the ADHD-SR scale were negatively correlated with the rsFC in the OFC, putamen, hippocampus, and lentiform nucleus (see Tables S28–S32).

DISCUSSION

The prevalence of adult ADHD has been demonstrated to be more than 5-fold higher in AUD patients than in the general population (Daigre et al., 2015; van Emmerik-van Oortmerssen et al., 2012; Huntley et al., 2012; Luderer et al., 2018). Past studies also asserted an AUD predisposition in ADHD individuals (Brinkman et al., 2015; Knop et al., 2009; Lee et al., 2011). An increased risk for SUD following ADHD was also supported by a longitudinal study (Wilens et al., 2011). However, others reported, that there was no increased risk of AUD in individuals with childhood ADHD that did not develop an SUD during adolescence (Levy et al., 2014). This study aimed to contribute to a better understanding of the neuronal connectivity impairments underlying this condition. Therefore, the hypotheses were supported in finding shared traits in the rsFC for both disorders that would explain the comorbidity prevalence. The group comparison analyses resulted in shared patterns of altered rsFC for all disorders.

Regarding the analysis of the DMN, the temporal lobe was observed to be a significantly affected area under both disorders, and thus also under comorbidity. Our results found increased connectivity from the PCC to the MTG, which is in line with previous findings (Müller-Oehring et al., 2015). The MTG is related to prospection thinking and mind-wandering by the use of past experiences (Hsu & Sonuga-Barke, 2016; Squire et al., 2004). Having experienced reward-related feelings after using alcohol might lead to a loss of control of individuals' thoughts in, for example, stressful situations or aversive events. These individuals then might become more likely to relapse. Moreover, significant results also included the inferior temporal gyrus (ITG). A study on healthy volunteers showed an increase of PCC–ITG connectivity (specifically to BA 20), after 90 minutes of acute alcohol intake (Weber et al., 2014). We observed the same increase in PCC-ITG connectivity in currently abstinent participants with AUD. This might indicate that the effect of acute alcohol intake on rsFC that was observed in healthy controls persists in currently abstinent individuals with AUD. Relating to the opponent-process theory by R. Solomon, the original, "normal," state of the PCC-ITG rsFC is altered in HC after acute intake of alcohol. However, this alteration becomes a chronic state in individuals with AUD and might characterize a neural correlate of alcohol tolerance, a main characteristic of the disorder. The ITG is functionally linked to the visual pathways, playing a key role in object recognition (Gross, 2008). The same altered connectivity has been reported for the ADHD group in our results, suggesting a higher cue reactivity in ADHD individuals after developing interest in alcohol or other substances. This consideration may explain that ADHD could aggravate the symptoms, recovery process, and relapse rate of SUD patients.

Additionally, enlarged rsFC to the SMG was observed in both ADHD and AUD groups compared to HC, which was further the case in the AUD + ADHD group. The SMG is part of the somatosensory association cortex and it seems to be involved in empathy and reading emotions on other people (Lawrence et al., 2006; Morishima et al., 2012; Silani et al., 2013), taking part in social behavior. Former studies have related reduced SMG cortical thickness in ADHD to inattentiveness (McLaughlin et al., 2014). Concerning AUD, a study of nalmefene effects in AUD patients described heightened activity in this area when viewing emotional faces, and increased activity in this region was linked to improved social cognition and emotion processing (Vollstädt-Klein et al., 2019). Our results may seem contrary to these former studies; however, the increased connectivity in the SMG within the DMN in our study was detected using a different approach. Under resting-state conditions, the abnormally high PCC-SMG connectivity may significate false self-awareness and/or excessive emotion sensitivity.

Compared to the HC, the AUD + ADHD group also displayed the previously described changes in rsFC in the DMN. Furthermore, we observed several brain regions (mainly BA 4 and BA 6) with decreased connectivity in this group that were not found in the AUD or the ADHD group when compared to HC. The BA 4 is located in the primary motor cortex, and the BA 6 comprises the premotor cortex and the SMA. All these structures are involved in movement control and coordination. Brain activity within these motor areas is functionally connected and highly correlated, even though each area has its own functions. Higher connectivity values to the primary motor cortex have been associated with impaired motor inhibition in ADHD subjects (Cortese et al., 2012). This enhanced connectivity to motor and executive control-related regions goes along with increased impulsivity rates, a main symptom of ADHD individuals. Impulsivity was first suggested as an SUD vulnerability marker (Verdejo-Garcia et al., 2008). Some studies have already pointed out the relationship between AUD and impulsivity (Bjork et al., 2004; Kamarajan et al., 2020; Zhu et al., 2017), also reporting a direct proportionality between the impulsivity scores and the frequency of alcohol intake (Weafer et al., 2011). Impulsivity was also suggested as the main ADHD trait to facilitate developing AUD (Daurio et al., 2018). Additionally, a correlation between higher impulsivity scores and decreased activation in the ventral striatum (an important region within the reward network) and in the ACC (an emotion cognitive-based control area) has been reported (Beck et al., 2009). Furthermore, a correlation of cue reactivity and the severity of nicotine dependence was observed in these motor regions (Smolka et al., 2006). Therefore, it can be concluded that AUD adds more difficulties to individuals with ADHD regarding inhibitory control and enhances impulsive behavior, leading to a significantly increased relapse risk in AUD + ADHD patients.

The analysis of DAN yielded the BA 6 as the mostly affected region of this network. Enhanced connectivity was observed for the AUD + ADHD and the ADHD groups compared to HC. This is in line with the results obtained from the DMN analysis, implicating a BA 6 dysregulation in ADHD that worsens when AUD is present. While performing cognitive tasks, the DMN activity is reduced and so is thus its inhibitory influence on task-related networks (Sonuga-Barke & Castellanos, 2007). The reduced rsFC of the DMN with the SMA might result in lower inhibition. In turn, this leads to higher rsFC of the DAN with the SMA. This dichotomy of the rsFC of the SMA produces an abnormal starting point for the DAN. Normally, activity within the DAN is enhanced while performing a task (Sonuga-Barke & Castellanos, 2007). However, due to the different starting point in individuals with AUD and ADHD, this network may become overactivated easily. Thus, the dysregulation of the DAN seems to be jointly responsible for the attention and inhibition deficits of ADHD and AUD.

Concerning the SN, our data showed connectivity impairments from the ACC to the PFC in all patient groups compared to HC. Past studies suggested that prefrontal dysfunction leads to impairments in the regulation of salient stimuli, and is therefore one of the main neurobiological factors of an SUD (Tarter et al., 2004). Other studies found PFC dysfunctions in ADHD (Bos et al., 2017) and more specifically in the OFC and the inferior PFC (Arnsten & Rubia, 2012; Rubia et al., 2010). The PFC in general has been linked to inhibition and salience modulation (Arnsten & Rubia, 2012; Cipolotti et al., 2016; Kalivas, 2008), and the OFC has been related to problems in impulse control and social disinhibition (Hesslinger et al., 2002). More studies have investigated these ADHD-related deficits, concluding that individuals with ADHD pay more attention to irrelevant visual stimuli even when they have received no attention indications (Sripada et al., 2014a; Tang et al., 2018). Our results showed a relation between ADHD and AUD concerning the ACC and PFC. This suggests impaired inhibition, which is a common characteristic in both disorders that could be enhanced in comorbid individuals. However, our results show the opposite, with the AUD + ADHD group displaying a smaller cluster of reduced connectivity than ADHD and AUD when compared to HC. With respect to the SN, our data underline once again previous observations of impairments in inhibitory control in ADHD. This might facilitate and reinforce alterations caused by AUD, with comorbid individuals becoming even more susceptible to salient stimuli.

Previously, the DMN has been considered as the most important network, when it comes to alterations regarding ADHD—however, both increased and decreased between-network connectivity have been observed. This might be due to different seeds or methods that have been used (Kaboodvand et al., 2020). Altered between-network rsFC, for example, regarding the SN or DMN, was also observed in AUD (Fede et al., 2019). Analyzing shared connectivity between networks has highlighted the alteration of the BA 6 under comorbid conditions. The three studied networks showed altered connectivity (decreased for the DMN and increased for the DAN and SN) to this area when compared to both HC and AUD. These findings amplify a possible impairment of the rsFC in the BA 6 that may have further repercussions in these patients. Also, this observation seems to be in line with the DMN and further networks being dysregulated in ADHD, even though a recent meta-analysis was not

able to fully clarify the relation of rsFC (using seed-based connectivity) and ADHD (Cortese et al., 2021). Also, the inverse relationship of the connectivity between the BA 6 to the DMN compared to the other 2 networks underlines the anticorrelation as a characteristic of the DMN (Uddin et al., 2009). Even though the implication of the SMG in is not well defined in AUD and ADHD, our results highlight its importance as a possible bridge between their shared cognitive and behavioral impairments since both disorders display alterations compared to HC. Interestingly, a stronger dysregulation was observed in the AUD + ADHD group also compared to AUD and ADHD regarding the SN. A dysregulation of the SN was reported previously as a link between ADHD and tobacco smoking (Janes et al., 2018). Even though causal interpretations still lack supporting data it, one might hypothesize that a dysregulation of the SN in ADHD may be considered as a risk factor for developing SUD.

Relating rsFC of the above-mentioned networks to clinical measures, our findings contribute to previous studies. Within and between connectivity of, besides others, the DMN and SN predict AUD severity, measured by the AUDIT (Fede et al., 2019). The connectivity analysis of the DMN in our study highlighted the alteration of the MTG in both AUD and ADHD, and under comorbidity conditions. These findings have been supported by a correlation analysis with the AUDIT and ADHD-SR scale that supports an increase of the connectivity in the area with higher scores in these tests. Moreover, our sample showed a correlation between the decreased connectivity of prefrontal regions in the SN and the scores of the AUDIT and the ADHD-SR scale. Regarding the DAN, correlation analyses supported the alteration of the BA 6 in the studied disorders. It has been reported that connectivity within this region is positively correlated with increased scores of the tests, thus supporting the idea that the combination of both disorders might result in an abnormally high connectivity toward this area. Further, an increase of rsFC in subcortical and motor regions was related to the severity of hyperactivity but not impulsivity in adults with ADHD (Sörös et al., 2019), while others observed a positive correlation with both hyperactive and impulsive measures in executive control and cerebellar regions (Mostert et al., 2016).

While results of the current study contribute to better understand the comorbidity of ADHD and AUD, several limitations need to be mentioned. Our small sample size limits the power of the results. The uneven distribution of individuals per group was also due to the included sample: The comorbid group resulted in a smaller sample due to excluding individuals with medication or consumption of cannabis. Also, not all participants filled out the questionnaires completely which led to a smaller sample for the correlation analyses. We did not conduct an interview on the total amount of alcohol intake during the months prior to study participation. This could have an influence on rsFC. In addition, we were not able to perform additional analyses regarding sex-differences. Even though the ratio of male to female was not significantly different between groups, the small number of females did not allow for further analyses. Further studies should not only consider these factors but also aim to address longitudinal questions in order to infer from correlational to causal explanations.

Concluding, our study provides first evidence for altered rsFC in ADHD and AUD comorbidity, with an approach to shared connectivity traits within the main networks involved in both disorders. The relationship between ADHD and AUD is suggested to be based on neural inhibitory deficits and cue reactivity. Individuals with ADHD might be more vulnerable to environmental cues than HC, making them more easily distracted also due to their inhibitory deficits. These deficits are based on impaired connectivity within the DAN and SN according to our results, but also on a previously described hyperactivity of the DMN. Distractibility, inattention, and impulsivity are the main behavioral traits that can be extracted from the alterations of these networks, turning ADHD into a risk factor for the development of SUD. Shared deficits of both disorders seem to be potentiated in comorbid individuals, with alterations in the rsFC possibly being one cause of these problems. Our observation further supports the hypothesis that ADHD individuals might be more vulnerable to developing an AUD. Thus, the diagnosis and treatment of ADHD during childhood or early adolescence could reduce the risk to develop a future AUD. When these individuals develop an AUD, impulsivity and inattention traits might worsen and thus may also increase the risk for the persistence of ADHD symptoms in adulthood. Still, the early use of other substances during adolescence might cause changes in the SN of ADHD individuals that facilitate future AUD, but further research is needed in this direction.

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CONFLICTS OF INTEREST

Mathias Luderer has received honoraria as a speaker and for participation in advisory boards from MEDICE / Arzneimittel Pütter GmbH and Shire / Takeda, and travel costs from Shire / Takeda. Esther Sobanski has received speaker's honoraria from Shire. All other authors state that they have no conflicts of interest.

AUTHORS CONTRIBUTION

SVK, ML, and ES were responsible for the study design. SG contributed to the acquisition of fMRI and psychometric data. AFC, SG, and SVK performed the data analysis. AFC and SG drafted the manuscript. SVK, FK, and ES procured study funding. All authors revised the manuscript critically for important intellectual content and approved the final version.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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